Published in final edited form as:
Cancer Causes Control. 2009 October ; 20(8): 1317–1325. doi:10.1007/s10552-009-9352-9.

Intake of folate, vitamins B6, B12 and methionine and risk of pancreatic cancer in a large population-based case-control study

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Abstract

Objective—Folate and other methyl-group nutrients may play a key role in pancreatic carcinogenesis through their effects on DNA integrity. We examined the association between pancreatic cancer and intake of folate, vitamins B6, B12 and methionine in a large population-based case-control study.

Methods—Risk factor data were collected during in-person interviews with 532 pancreatic cancer cases diagnosed in 1995-1999 and 1701 frequency-matched controls in the San Francisco Bay Area. Dietary history and supplement use were obtained using a semi-quantitative food frequency questionnaire developed at Harvard University. Adjusted unconditional logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) as estimates of the relative risk.

Results—Total folate intake was inversely associated with pancreatic cancer (5^{th} vs. 1^{st} quintile: OR=0.67, 95% CI=0.48-0.93, P_{trend}=0.04). Increased vitamin B12 from food was positively associated with pancreatic cancer although risk estimates for quintiles 3 to 5 were similar (5^{th} vs. 1^{st} quintile: OR=1.9, 95% CI=1.3-2.6, P_{trend}=0.001). Intake of vitamin B6 or methionine was not associated with pancreatic cancer risk.

Conclusions—Our study provided some support for an inverse association between folate intake and pancreatic cancer risk. The increased pancreatic cancer risk with vitamin B12 intake from food warrants further investigation.

Keywords

Pancreatic neoplasms; diet; micronutrients; folic acid; case-control studies

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in U.S. men and women and caused an estimated 34,290 deaths in 2008 [1]. The prognosis of pancreatic cancer remains extremely poor, with a 5-year survival rate of less than 5% [2]. Symptoms typically are non-specific and vague, contributing to the difficulty in diagnosing pancreatic cancer at an early

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stage when the disease is more treatable. The recent SEER statistics show that only 7% of patients have localized disease at diagnosis reflecting the lack of established screening tests and known risk factors to identify those at high risk [3]. Family history has been associated with an approximate 2-fold increased risk of pancreatic cancer [4] similar to that of cigarette smoking, the only consistently identified modifiable risk factor. However, heredity has been estimated to account for about 5-10% [5] and cigarette smoking for approximately 25-30% of all pancreatic cancer cases [6]. Recent studies have suggested that modifiable dietary factors, high intake of vegetables and fruits, may decrease risk of pancreatic cancer [7-10]. Dietary folate has been hypothesized as a possible mechanism to explain these associations [11].

Folate has been implicated in cancer etiology because of its vital role in DNA methylation, nucleotide synthesis, and DNA replication and repair [11-14]. For example, folate may influence gene stability and expression through its essential role in methionine synthesis and in the conversion to *S*-adenosylmethionine (SAM, the universal donor for DNA methylation) [13,15]. Other nutrients that play a key role in folate-mediated methyl-group metabolism include vitamins B6 and B12, important enzymatic cofactors, and the essential amino acid, methionine, a key intermediary compound [16]. Thus, deficiencies in folate and other methyl-group nutrients may increase the risk of pancreatic cancer through altered methylation of DNA and RNA, disruption of DNA integrity and DNA repair, and increased DNA damage and gene mutations [14,17]. However, results have been inconsistent in the few studies that have examined the association between pancreatic cancer risk and intake of folate [18-24], B6 [18,20,24,25], B12 [18,20,23,24], and methionine [20,21,25]. Interestingly, several cohort studies also analyzed serum or plasma folate levels in participants with results suggesting an inverse dose-response consistent with food-related folate results [23] or limited to nonusers of multivitamins [24].

We examined the relationship among folate, vitamin B6, vitamin B12, and methionine and pancreatic cancer risk in our large population-based case-control study conducted in the San Francisco Bay Area. The large study size (532 cases, 1701 controls) and availability of extensive risk factor data allowed us to assess potential confounders and effect modifiers [26-28] that may have contributed to the inconsistency of results reported in earlier studies.

MATERIALS AND METHODS

Study population

Details of the study methods and population characteristics have been described previously [7,29,30]. In brief, cases with incident adenocarcinoma of exocrine pancreas diagnosed between 1995 and 1999 were identified using rapid case ascertainment conducted by the Northern California Cancer Center. Eligible cases were 21–85 years old, residents of one of six San Francisco Bay Area counties at diagnosis/interview, alive and able to complete an in-person interview in English. Pancreatic cancer diagnoses were confirmed by the patients' physicians and by abstracts from the Surveillance, Epidemiology and End Results (SEER). Among the 798 eligible cases, 532 completed the interview for a response rate of 67%. Control participants were frequency-matched to cases by sex, 5-year age group and county and were selected from the target population using random-digit-dial (RDD). Identification of controls greater than 65 years old was supplemented by random sampling of the Health Care Finance Administration (now Center for Medicare and Medicaid Services) lists. Among the 2,525 eligible controls, 1,701 completed the interview for a response rate of 67%.

Data collection

Detailed data including age, race, education, diabetes status, history of smoking, alcohol consumption, physical activity and anthropometric measures were collected by trained interviewers during in-person interviews. No proxy interviews were conducted. The study was reviewed and approved by the University of California San Francisco Committee on Human Research. Signed informed consent was obtained from each participant prior to interview.

Dietary history was assessed using the validated 131-item semi-quantitative food-frequency questionnaire (FFQ) developed at Harvard University [31-36]. The FFQ scantron forms were processed by the Department of Nutrition at Harvard School of Public Health to create the dietary database that also contained the computed nutrient intake values. Participants were asked to report their average frequency of consumption of specific foods during the one year before diagnosis (cases) or interview (controls). Portion size was included either as part of the question or of the response, e.g. 1cup, 1oz., 1 glass, 2-4 glasses. Dietary supplement use also was assessed and included commonly used multivitamin and individual vitamin or mineral supplements. Intake of folate and of vitamin B6 supplements was computed by summing the amount contributed from single supplements and from multivitamins. Use of individual vitamin B12 supplements was not ascertained, thus vitamin B12 supplement intake was based on multivitamin use only. Nutrient intake was computed by multiplying the frequency of each food item by the nutrient content of the standard portion size specified for each food item. Food nutrient content values used to compute total nutrient intake were obtained from the Harvard University food composition relational database that was updated over time with data from U.S. Department of Agriculture sources [37].

Statistical methods

We computed odds ratios (OR) and 95 percent confidence intervals (CI) as estimates of the relative risk using adjusted unconditional logistic regression methods. Results from models stratified by sex were similar for men and women, therefore the results were combined. Linear trends in effect estimates were based on the chi-square statistic for the factor of interest when included as an ordinal variable in the adjusted unconditional logistic regression model [38]. All models were adjusted for the frequency-matched variables of age and sex.

In the analyses, total nutrient intake and nutrient intake from food were adjusted for total energy intake using the residual method [39] and were categorized into quintiles based on the distribution for each nutrient among the controls. For comparability with other studies and our previous analyses of nutrient data in this study, we first present results from parsimonious models adjusted for age, sex and total energy intake. Final multivariable models were additionally adjusted for usual adult BMI (<25, 25-<30, and ≥30 kg/m^2), history of diabetes, smoking (never smoker, former cigarette smoker who had quit [2 groups] >15 years before diagnosis/interview or 1-15 years before diagnosis/interview, current cigarette smoker or former smoker who had quit <1 year before diagnosis/interview, and pipe and/or cigar smoker), and alcohol consumption (lifelong never drinkers, ≤7, 8-14, 15-21, and >21 drinks per week). Other potential confounding factors, race (white, black/ African American, Asian/Pacific Islanders, or “other”), education (<high school, high school, college, and graduate work), and physical activity (30-minute recreational physical activity: ≤1/month, 2-4/month, 2-3/week, and ≥4/week) did not alter the main effect estimates for dietary factors of interest and therefore were not included in the final models.

The associations among folate and other folate-related methyl group nutrients with risk of pancreatic cancer were examined by smoking status (never vs. ever), by alcohol consumption (0-1 drink/day vs. >1 drink/day), and by level of methionine intake (low: quintiles 1-3 vs. high: quintiles 4-5). We formally tested for two-way statistical interaction between dietary factors and the dichotomously grouped variables using a chi-square test for the difference in the -2 log-likelihood ratio statistics computed from the models with and without the cross-product terms.

All statistical tests were two-sided and considered statistically significant for $p<0.05$ and somewhat or borderline significant for p-values ≥ 0.05 and ≤ 0.10. Statistical analyses were conducted using SAS software V9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Median age at diagnosis for pancreatic cancer patients in our study population was 65 years (data not shown), and consistent with registry data, there was a slightly greater proportion of men than women cases. The distribution of demographic and other selected factors in Table 1 differed somewhat by case-control status.

Analyses showed that total folate intake was associated with a reduced risk of pancreatic cancer (Table 2). Compared with the lowest quintile, those with the highest quintile of intake had a decreased risk of pancreatic cancer (OR=0.67, P_{trend}=0.04). Increased folate intake from food alone was associated with a somewhat decreased trend in ORs (P_{trend} =0.10) although the OR estimates for each quintile of folate were not different from unity. There was no association between total intake of vitamin B12 and pancreatic cancer risk. However, risk of pancreatic cancer was increased for those with the highest food-related vitamin B12 intake (OR=1.9, P_{trend}=0.001; Table 2). Estimates for vitamin B12 were not altered in models that also were adjusted for meat, eggs and dairy (food sources of vitamin B12), or that were mutually adjusted for folate intake. We also observed no association between pancreatic cancer risk and intake of vitamin B6 (total or food alone) or of methionine from food alone.

There was little evidence to suggest that intake of folate, vitamin B6 or B12 from supplements was associated with pancreatic cancer risk (data not shown). Risk estimates for pancreatic cancer were decreased somewhat with increased folate (P_{trend} =0.06), or vitamin B6 (P_{trend} =0.08) from supplements, although the individual estimates for the categories of nutrient-specific intake were similar and confidence intervals included unity (data not shown). When analyses were restricted to participants who did not use the specific nutrient supplement, results from the nutrient-specific analyses were similar to the results from analyses that included the supplement users (data not shown).

There was no evidence of statistical interaction for total intake of specific nutrients with smoking status, alcohol consumption or methionine intake (all $P_{interaction}$>0.12). However, the results from stratified analyses showed that the reduced risk of pancreatic cancer associated with total folate intake was somewhat stronger among never smokers, among those who consumed 0-1 alcoholic drink/day, and among those who had higher methoinine intake, particularly among those with the highest total folate intake (Table 3).

DISCUSSION

In this large population-based study, our results suggested that total folate intake was associated with a decreased risk of pancreatic cancer. Higher folate intake from food or from supplements was associated with similar modest lower risk estimates for pancreatic cancer. In addition, an increased risk estimate for pancreatic cancer was observed among those with

higher vitamin B12 intake from food. Results from stratified analyses suggested that the inverse association between total folate intake and pancreatic cancer was somewhat stronger among never smokers, those who consumed ≤1 alcoholic drink/day, or those with a high level of food-related methionine intake.

Results have been inconsistent from the few epidemiologic studies that have examined the role of dietary folate and risk of pancreatic cancer [18-24]. In the published case-control studies, dietary folate was associated with a reduced risk of pancreatic cancer in the Australian study [18], whereas no association was observed in the U.S. study [19]. In contrast, results were somewhat consistent across the several prospective cohort studies [20-22], where similar to our findings, a reduced risk of pancreatic cancer was observed with higher folate intake from food alone [20-22]. However, results related to total folate intake or folate from supplements were inconsistent across these studies with report of a non-significant increased risk for folate supplement use in Finnish male smokers [20], no association with total folate or use of folate supplements in the pooled analysis of two U.S. studies [21], and an inverse association with total folate, but no association with use of folate supplements in the pooled analyses of two Swedish studies [22]. Interestingly, results from analyses of serum or plasma folate levels in participants from several of these cohort studies were somewhat consistent with the results for dietary measures of folate. An inverse dose-response between serum folate and pancreatic cancer among the cohort of male smokers in Finland [23] was consistent with the food-related folate results [20], whereas a suggestive inverse trend between plasma folate levels and pancreatic cancer among participants in four large U.S. cohort studies was limited to nonusers of multivitamins [24], similar to the dietary results from two of these four studies [21].

Alcohol consumption and cigarette smoking can affect folate absorption and metabolism [26-28,40], and thus could increase the requirement for folate intake. Alcohol consumption has been shown to modify the association between folate and risk of colon [41] and breast cancer [42]. Similar to several earlier pancreatic cancer studies [20-22], we found no evidence of an overall interaction between alcohol consumption or cigarette smoking and folate intake in relation to pancreatic cancer risk. However, results from our stratified analyses suggested that the reduced risk may be somewhat stronger in never smokers or those who consumed an average of ≤1 alcoholic drink per day. It is possible that the increased risk associated with smoking or drinking overrides the risk reduction related to higher folate intake in these subgroups. Given that the small number of current smokers or heavy drinkers in our study limited our ability to further examine the intriguing results from our stratified analyses, further investigation is warranted in larger pooled studies.

Overall, the few studies that have examined vitamin B6 and pancreatic cancer risk [18,20,24,25] do not provide support of an association. Consistent with our null findings, two cohort studies [20,25] reported no association between vitamin B6 and pancreatic cancer, whereas results from a small case-control study showed an inverse association [18]. The one study that evaluated plasma levels of vitamin B6 and pancreatic cancer risk showed a somewhat inverse association only among nonusers of multivitamins [24].

Some support for our result showing a modest increased risk of pancreatic cancer with higher vitamin B12 intake from food is provided by other studies of pancreatic cancer [18,23] and studies of other cancers including prostate [43,44], esophageal and gastric cancer [45]. Vitamin B12 intake from food is derived almost exclusively from animal sources, such as meat, milk, and eggs. It is possible that vitamin B12 may be a proxy for other factors or nutrients or a measure of intake of these foods. However, positive associations were not attenuated with additional adjustment of intake of meat, eggs, dairy products, total or saturated fat. The observed increased risk also may be a result of

unmeasured confounding. For example, heterocyclic amines formed in meats that are cooked at high temperatures have been associated with increased pancreatic cancer risk [46,47]. However, we were unable to determine the effect of cooking methods on the association with vitamin B12 as cooking method data were not collected in our study. These associations require further examination in large pooled studies that can assess vitamin B12 from multiple sources and evaluate other potential confounders and effect modifiers in detail such as the effect of cooking methods.

In a Medline search of articles published in English, we found three cohort studies that had evaluated the association between pancreatic cancer and methionine intake [20,21,25]. Consistent with our results, two of these studies reported no association with methionine intake [20,21], whereas a pooled analysis of two Swedish studies showed a strong decreasing trend in risk (P_{trend} =0.0005)[25]. Methionine is critical in the production of *S*-adenosylmethionine, an important methyl donor for DNA methylation. Folate plays an integral role in the remethylation of homocysteine to methionine. If methionine levels are low, more folate may be needed as methyltetrahydrofolate to form methionine. Therefore, it is plausible that methionine levels could modify an association between folate and pancreatic cancer. Our results and those from two U.S. cohort studies [21] found no overall evidence of a significant interaction between folate and methionine intake related to pancreatic cancer. In contrast, results from the pooled Swedish cohorts [25] showed that those with high intake of folate and high intake of methionine had the greatest reduced risk of pancreatic cancer. Interestingly, although there was no overall interaction between methionine and folate intake in our study population, the results from our folate analyses stratified by low and high methionine intake supported the results reported in the Swedish cohort study. Further investigation in large pooled studies is needed to elucidate these findings and to assess whether methionine alters the association between folate intake and pancreatic cancer.

Overall, the results from our and other published studies suggest that high folate intake may be associated with a decreased risk of pancreatic cancer. However, despite some similarities across studies, the underlying differences in study designs, study populations, and classification of folate and other nutrients make a summary interpretation of the literature on folate and B vitamins difficult. Results from two of the three cohort studies may not be generalizable to the general population given that one study was conducted among a cohort of Finnish male smokers and the other among cohorts of U.S. nurses and health professionals [20, 21]. In addition, results from most studies were based on a small number of cases (typically < 200 cases). Differences in dietary habits and patterns across study populations also were likely to have contributed to observed discrepant results e.g. the Swedish study population had on average a lower rate of folate supplement use and lower folate status than those of the published U.S. populations [22]. These differences suggest that strong associations may be detectable only in populations that include a large number of participants with low folate status (e.g. <200ug/day, the cutpoint for the reference group used in the Swedish cohorts). Thus, based on the current published literature, large and well-designed studies are needed to clarify the role that folate and other B-vitamins (from food and from supplements) play in risk of pancreatic cancer.

This large population-based study included 532 pancreatic cancer cases, the largest number of cases in the published studies that have examined the effect of methyl-group nutrients on pancreatic cancer. Rapid case ascertainment with a goal to identify eligible cases within one month of diagnosis was used to reduce selection bias and to diminish the effects of the short survival and high mortality rates on patient recruitment. We also had a low refusal rate of 8% among the cases. However, given the high fatality of pancreatic cancer, if patient participants were healthier and therefore more likely to have better diets with resultant

higher levels of nutrient intake than not interviewed patients, then our results may be biased toward the null. Extensive data were collected during in-person interviews by trained interviewers, eliminating information bias associated with use of proxy data and enabling us to consider numerous potential confounders and effect modifiers in our analyses. To help minimize the effects of reverse causation and recall bias, participants were asked to report their usual diet a year prior to diagnosis (cases) or interview (controls) and were provided with food models for serving sizes, and the FFQ also was administered in a consistent manner by a trained interviewer. In addition, we collected data about dietary changes over the past ten years and found no evidence that cases were more likely to change their diet than were controls [7]. However, when answering specific dietary questions, it is possible that cases and controls who had experienced dietary changes may have differentially reported these changes. If cases were more likely to have reported decreased consumption of some foods then our results may have been biased away from the null, whereas if dietary changes were subtle and gradual among cases due to their disease then dietary recall may not accurately have reflected a change and our results may be biased toward the null.

In conclusion, our results have provided evidence that high folate intake is associated with a decreased risk of pancreatic cancer although there was no evidence of an association with intake of other nutrients important in methyl-group metabolism such as vitamin B6 and methionine. The increased risk estimate for pancreatic cancer associated with higher intake of vitamin B12 from food requires confirmation and additional investigation in future studies.

Acknowledgments

Grant Support:

This work was supported in part by National Cancer Institute grants CA59706, CA108370, CA109767, CA89726 (E.A. Holly, PI) and by the Rombauer Pancreatic Cancer Research Fund. The collection of cancer incidence data for the UCSF study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

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Table 1

Demographic, health, and lifestyle characteristics of 532 cases and 1701 controls in a population-based study for pancreatic cancer, San Francisco Bay Area, California*

Characteristics	Cases n (%)	Controls n (%)
Age (yrs)		
<50	46 (9)	164 (10)
50-59	120 (23)	438 (26)
60-69	172 (32)	473 (28)
70-79	158 (30)	498 (29)
≥80	36 (7)	128 (8)
Sex		
Male	291 (55)	883 (52)
Female	241 (45)	818 (48)
Race		
White	442 (83)	1471 (86)
Black/African American	46 (9)	78 (5)
Asian or Pacific Islander	35 (7)	119 (7)
Others	9 (2)	33 (2)
History of diabetes		
Yes	76 (14)	161 (10)
Body mass index (kg/m^2)		
<25	281 (53)	999 (59)
25-<30	197 (37)	553 (32)
≥30	54 (10)	149 (9)
Smoking		
Non-smoker	163 (31)	652 (38)
Former smoker, quit >15 yrs	133 (25)	508 (30)
Former smoker, quit 1-15 yrs	89 (17)	261 (15)
Current smoker & quit <1 yr	131 (25)	207 (12)
Pipe/cigar smoker	16 (3)	73 (4)
Alcohol drinking		
Never drinkers	85 (16)	305 (18)
≤7 drinks/wk	231 (44)	804 (47)
8-14 drinks/wk	83 (16)	293 (17)
15-21 drinks/wk	39 (7)	138 (8)
>21 drinks/wk	91 (17)	161 (9)

*Numbers (percentage) may not add up to the total number because of missing values or rounding

Table 2

Odds Ratios (OR) and 95% confidence intervals (CI) for risk of pancreatic cancer by quintiles of folate, vitamins B6, B12, and methionine intake in a population-based case-control study, San Francisco Bay Area, California

Nutrients Quintiles	Cases n (%)	Controls n (%)	OR† (95% CI)	OR‡ (95% CI)
Total folate (food and supplements), μg/day				
Q1 (<280)	135 (26)	340 (20)	1.0	1.0
Q2 (280-<363)	100 (19)	341 (20)	0.69 (0.51-0.94)	0.72 (0.53-0.98)
Q3 (363-<533)	114 (22)	340 (20)	0.78 (0.58-1.05)	0.86 (0.64-1.2)
Q4 (533-<738)	102 (19)	340 (20)	0.70 (0.52-0.95)	0.76 (0.56-1.04)
Q5 (≥738)	74 (14)	340 (20)	0.57 (0.41-0.79)	0.67 (0.48-0.93)
P-trend			.002	0.04
Folate from food only, μg/day				
Q1 (<247)	135 (26)	340 (20)	1.0	1.0
Q2 (247-<295)	112 (21)	341 (20)	0.77 (0.57-1.04)	0.82 (0.61-1.1)
Q3 (295-<338)	98 (19)	339 (20)	0.70 (0.51-0.94)	0.78 (0.57-1.1)
Q4 (338-<396)	89 (17)	340 (20)	0.64 (0.47-0.87)	0.74 (0.53-1.0)
Q5 (≥396)	91 (17)	341 (20)	0.66 (0.49-0.91)	0.79 (0.57-1.1)
P-trend			0.004	0.10
Total vitamin B6 (food and supplements), mg/day				
Q1 (<1.9)	118 (22)	341 (20)	1.0	1.0
Q2 (1.9-<2.4)	114 (22)	340 (20)	0.93 (0.74-1.2)	0.97 (0.71-1.3)
Q3 (2.4-<3.7)	117 (22)	340 (20)	0.92 (0.49-0.87)	1.0 (0.75-1.4)
Q4 (3.7-<5.0)	98 (19)	340 (20)	0.81 (0.43-0.77)	0.90 (0.65-1.2)
Q5 (≥5.0)	78 (15)	340 (20)	0.67 (0.43-0.77)	0.76 (0.55-1.1)
P-trend			0.01	0.12
Vitamin B6 from food only, mg/day				
Q1 (<1.7)	114 (22)	341 (20)	1.0	1.0
Q2 (1.7-<1.9)	103 (20)	340 (20)	0.86 (0.63-1.2)	0.89 (0.64-1.2)
Q3 (1.9-<2.2)	106 (20)	340 (20)	0.90 (0.66-1.2)	0.99 (0.72-1.4)
Q4 (2.2-<2.5)	101 (19)	340 (20)	0.87 (0.64-1.2)	0.97 (0.70-1.3)
Q5 (≥2.5)	101 (19)	340 (20)	0.92 (0.67-1.3)	1.0 (0.75-1.4)
P-trend			0.65	0.68
Total vitamin B12 (food and supplements), mg/day				
Q1 (<4.2)	84 (16)	341 (20)	1.0	1.0
Q2 (4.2-<6.4)	116 (22)	340 (20)	1.3 (0.96-1.8)	1.4 (0.97-1.9)
Q3 (6.4-<10.1)	113 (22)	340 (20)	1.3 (0.94-1.8)	1.4 (0.99-1.9)
Q4 (10.1-<14.5)	106 (20)	340 (20)	1.3 (0.91-1.8)	1.3 (0.93-1.8)
Q5 (≥14.5)	106 (20)	340 (20)	1.3 (0.90-1.7)	1.3 (0.92-1.8)
P-trend			0.31	0.26
Vitamin B12 from food only, mg/day				
Q1 (<3.4)	66 (13)	341 (20)	1.0	1.0

Nutrients Quintiles	Cases n (%)	Controls n (%)	OR† (95% CI)	OR‡ (95% CI)
Q2 (3.4-<4.4)	86 (16)	339 (20)	1.3 (0.94-1.9)	1.3 (0.92-1.9)
Q3 (4.4-<5.6)	123 (23)	340 (20)	1.8 (1.3 -2.6)	1.8 (1.3 -2.5)
Q4 (5.6-<7.5)	115 (22)	341 (20)	1.8 (1.2 -2.5)	1.7 (1.2 -2.5)
Q5 (≥7.5)	135 (26)	340 (20)	2.1 (1.5 -2.9)	1.9 (1.3 -2.6)
P-trend			<0.001	0.001
Methionine intake, mg/day				
Q1 (<1443)	101 (19)	341 (20)	1.0	1.0
Q2 (1443-<1634)	101 (19)	340 (20)	0.96 (0.70-1.3)	1.0 (0.73-1.4)
Q3 (1634-<1830)	125 (24)	339 (20)	1.2 (0.88-1.6)	1.3 (0.92-1.7)
Q4 (1830-<2060)	95 (18)	340 (20)	0.94 (0.68-1.3)	1.0 (0.74-1.4)
Q5 (≥2060)	103 (20)	341 (20)	1.0 (0.75-1.4)	1.1 (0.77-1.5)
P-trend			0.90	0.69

† Adjusted for age (in 5-year group), sex, and total energy intake (quartiles)

‡ Additionally adjusted for body mass index, history of diabetes, smoking, and alcohol consumption.

Table 3

Odds Ratios (OR) and 95% confidence intervals (CI) for risk of pancreatic cancer by quintiles of daily total folate intake stratified by smoking, alcohol, and methionine in a population-based case-control study, San Francisco Bay Area, California

Folate intake, Quintiles (μg/day)	Cases n (%)	Controls n (%)	OR† (95% CI)	OR‡ (95% CI)
Smoking status				
Never smokers				
Q1 (<280)	40 (25)	123 (19)	1.0	1.0
Q2 (280-<363)	38 (23)	118 (18)	0.92 (0.55-1.6)	0.85 (0.50-1.4)
Q3 (363-<533)	35 (21)	139 (21)	0.70 (0.41-1.2)	0.70 (0.41-1.2)
Q4 (533-<738)	30 (18)	131 (20)	0.66 (0.38-1.1)	0.69 (0.40-1.2)
Q5 (≥738)	20 (12)	141 (22)	0.42 (0.23-0.76)	0.43 (0.24-0.80)
P-trend			0.002	0.007
Ever smokers				
Q1 (<280)	95 (26)	217 (21)	1.0	1.0
Q2 (280-<363)	62 (17)	223 (21)	0.59 (0.40-0.86)	0.58 (0.40-0.85)
Q3 (363-<533)	79 (22)	201 (19)	0.84 (0.58-1.2)	0.87 (0.60-1.2)
Q4 (533-<738)	72 (20)	209 (20)	0.73 (0.51-1.1)	0.72 (0.49-1.0)
Q5 (≥738)	54 (15)	199 (19)	0.66 (0.44-0.98)	0.70 (0.47-1.0)
P-trend			0.13	0.20
P for interaction			0.11	0.12
Alcohol intake				
0-1 drink/day				
Q1 (<280)	84 (27)	219 (20)	1.0	1.0
Q2 (280-<363)	58 (19)	222 (20)	0.61 (0.41-0.91)	0.61 (0.41-0.90)
Q3 (363-<533)	70 (22)	218 (20)	0.74 (0.50-1.1)	0.78 (0.53-1.2)
Q4 (533-<738)	52 (17)	217 (20)	0.54 (0.36-0.82)	0.55 (0.37-0.84)
Q5 (≥738)	49 (16)	233 (21)	0.54 (0.36-0.80)	0.57 (0.38-0.87)
P-trend			0.003	0.01
>1 drink/day				
Q1 (<280)	50 (24)	121 (20)	1.0	1.0
Q2 (280-<363)	42 (20)	119 (20)	0.80 (0.49-1.3)	0.91 (0.55-1.5)
Q3 (363-<533)	44 (21)	122 (21)	0.89 (0.54-1.5)	1.05 (0.63-1.8)
Q4 (533-<738)	48 (23)	123 (21)	0.88 (0.54-1.4)	1.1 (0.66-1.8)
Q5 (≥738)	25 (12)	107 (18)	0.59 (0.34-1.0)	0.76 (0.42-1.3)
P-trend			0.16	0.69
P for interaction			0.54	0.35
Methionine intake, mg/day				
Low (<1730)				
Q1 (<280)	88 (27)	214 (21)	1.0	1.0
Q2 (280-<363)	60 (18)	213 (21)	0.65 (0.44-0.95)	0.69 (0.46-1.0)
Q3 (363-<533)	73 (22)	199 (20)	0.83 (0.57-1.2)	0.91 (0.62-1.3)

Folate intake, Quintiles (μg/day)	Cases n (%)	Controls n (%)	OR† (95% CI)	OR‡ (95% CI)
Q4 (533-<738)	59 (18)	200 (20)	0.69 (0.47-1.0)	0.75 (0.50-1.1)
Q5 (≥738)	47 (14)	194 (19)	0.63 (0.42-0.95)	0.74 (0.48-1.1)
P-trend			0.05	0.25
High (≥1730)				
Q1 (<280)	47 (24)	126 (19)	1.0	1.0
Q2 (280-<363)	40 (20)	128 (19)	0.78 (0.47-1.3)	0.79 (0.47-1.3)
Q3 (363-<533)	41 (21)	141 (21)	0.75 (0.45-1.2)	0.81 (0.48-1.4)
Q4 (533-<738)	43 (22)	140 (21)	0.79 (0.48-1.3)	0.87 (0.51-1.5)
Q5 (≥738)	27 (14)	146 (21)	0.50 (0.29-0.85)	0.56 (0.32-0.97)
P-trend			0.02	0.09
P for interaction			0.49	0.66

†Adjusted for age (in 5-year group), sex, and total energy intake (quartiles)

‡Additionally adjusted for body mass index, history of diabetes, smoking (not included in analyses stratified by smoking), and alcohol consumption (not included in analyses stratified by alcohol intake)